Amendments to the Sequence Listing:

Please replace the sequence listing, filed on October 14, 2005, in the present application, with the sequence listing appended hereto.

REMARKS

Applicants acknowledge receipt of the Office Action dated November 27, 2006 (hereinafter "the Office Action"). Reconsideration of the present application is respectfully requested in view of the foregoing amendments and the remarks which follow.

I. Status of the Claims

Following the above amendments, claims 20-27 and 39-43 are pending, with claims 20, 24 and 38 being the independent claims. Solely to advance prosecution, and without acquiescing to the rejections, amendment is sought to claims 20-27 and 39-43, and previously withdrawn claims 28-38 have been canceled. Claims 1-19 were previously canceled.

Support for the amendments to claims 20-27 and 39-43 may be found in the specification and originally-filed claims. Claim 20 incorporates elements from previous claims 20, 28 and 32, and is supported by the specification at: page 3, lines 23-27; and page 3, line 33 to page 4, line 1. The amendment to claims 21 and 25 is supported by the specification at page 2, line 32. Claim 24 incorporates elements from previous claims 20, 28 and 32. Additional amendments have been made to correct minor errors and to further define the presently claimed invention. Accordingly, these amendments do not introduce new matter and their entry and consideration is respectfully requested.

II. Objection to Specification

At page 4 of the Office Action, the PTO has objected to the specification because pages 21-23 and Figure 1 lack appropriate sequence identifiers. Applicants have amended the specification to recite sequence identifiers, and have provided a substitute sequence listing in both paper and computer-readable form. These amendments are fully supported by the specification as filed, and do not introduce new matter. Furthermore, the paper and the disk copy are identical. 37 C.F.R. § 1.825. Applicants respectfully believe that the present application complies with 37 C.F.R. §§ 1.821-1.825, and request withdrawal of the objection

III. Response to Arguments/Election/Restriction

At page 3 of the Office Action, the PTO reasserts restriction/unity of invention requirement, limiting the claims to a single sequence. The Examiner notes that the present application was not filed under 35 U.S.C. § 111 but is a national phase application under 35 U.S.C. § 371. Applicants continue to ***traverse*** the restriction to a single species, as Applicants are entitled to consideration of at least ten (10) species in national phase applications. In "Examination of Patent Applications Containing Nucleotide Sequences," 1192 O.G. 68 (November 19, 1996), the Director partially waived the requirement of restriction under 37 C.F.R. § 1.141 *and also* the unity of invention standard of 37 C.F.R. §§ 1.475 and 1.499 *et seq.*

> The Commissioner has decided sua sponte to partially waive 37 CFR 1.475 and 1.499 et seq. to permit applicants to claim up to ten (10) nucleotide sequences which do not have the same or corresponding special technical feature, without the payment of an additional fee. The PCT permits inventions which lack unity of invention to be maintained in the same international application for the payment of additional fees. Thus, in international applications, for each group for which applicant has paid additional international search and/or preliminary examination fees, the PTO has determined that up to four (4) such additional sequences per group is a reasonable number for examination. Further, claims directed to the selected sequences will be examined with claims drawn to any sequence combinations which have a common technical feature with the selected sequences. Nucleotide sequences encoding the same protein are considered to satisfy the unity of invention standard and will continue to be examined together.

Accordingly, Applicants are *entitled* to consideration of *at least ten independent and distinct species*, and can obtain consideration of additional species with the payment of a fee. Moreover, SEQ ID NOs:1, 3, 5 and 7 are related, as are SEQ ID NOs:2, 4, 6 and 8. Accordingly, a search for art relevant to one sequence will find art relevant to 3 other sequences. For at least these reasons, Applicants respectfully request reconsideration and withdrawal of the restriction limiting the search to a single species.

IV. Claim Objections

In the Office Action, the PTO has set forth a number of objections which Applicants summarize below:

At page 4, claims 22 and 26 objected under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim;

At page 4, claims 22 and 26 objected under 37 C.F.R. § 1.75 as being substantial duplicates of claims 20 and 24;

At page 5, claims 20, 24, 37-38, and 43 objected for containing non-elected subject matter;

At page 5, claim 24 objected because the hyphen between "therapy" and "resistant" is omitted;

At page 5, claim 43 objected because a comma between "9" and "a pharmaceutically" is omitted

At page 4 of the Office Action, claims 22 and 26 objected under 37 C.F.R. § 1.75(c) as being of improper dependent form for failing to further limit the subject matter of a previous claim.

In view of the foregoing amendments to the claims, it is believed that these rejections have been accommodated. Applicants respectfully request withdrawal of the objections.

V. Rejections Under 35 U.S.C. § 112

In the Office Action the PTO has set forth a number of rejections under 35 U.S.C. § 112. In view of the foregoing amendments to the claims, it is believe that these rejections have been accommodated, rendered moot or overcome. Applicants will address the Examiner's comments as they may have been applied to presently pending claims 20-27 and 39-43.

A. At page 5 of the Office Action claims 20-22 and 41-42 have been rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which applicants regard as the invention. These rejections have been accommodated by amendments to the claims.

B. At page 7 of the Office Action, claims 20-27 and 37 have been rejected under 35 U.S.C. § 112, first paragraph, because the specification allegedly does not enable one skilled in the art to use the invention commensurate in scope with the claims. One element of the Examiner's rejection is that recitation of "a fragment thereof" broadens the scope of the claims to impermissibly exceed that which is reasonably enabled by the specification. This rejection is rendered moot by cancellation of the language which forms the basis of this aspect of the rejection.

An additional basis of rejection is the Examiner's observation that the claims encompass *in vivo* and *in vitro* methods using siRNA derived from SEQ ID NO:2, but the specification describes experiments performed *in vitro* with SEQ ID NO:4. First, Applicants note the relationship between SEQ ID NO:4 and SEQ ID NO:2, such that the person of ordinary skill would consider that the results observed with SEQ ID NO:4 provide sufficient enablement for a sequence comprising SEQ ID NO:2. Indeed, SEQ ID NO:4 is within the genus of sequences comprising SEQ ID NO:2.

As to the use of vectors other than pSUPER for RNAi, RNAi has been demonstrated with other vectors before the filing date of the present application. *See, e.g.* Miyagishi *et al.*, "Development and application of siRNA expression vector," *Nucleic Acids Res.* 2: 113-114 (2002) (Exhibit A).

As to the relationship between *in vitro* and *in vivo* data, the Examiner presents arguments that there may not be an exact correlation between *in vitro* results and claimed *in vivo* results. However, a rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985). Applicants further note that *in vitro* data may be sufficient to enable claims to *in vivo* embodiments. *See In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). Moreover, even *if* some *in vivo* embodiments would be inoperative, this would not be determinative, as the presence of inoperative embodiments does not destroy enablement of a claim. *Atlas Powder Co. v. E.I. du Pont de Nemours & Co.*, 750 F.2d 1569, 1577, 224 USPQ 409, 414 (Fed. Cir. 1984).

For at least these reasons, Applicants respectfully request reconsideration and withdrawal of the rejection.

C. At page 10 of the Office Action claims 38-43 have been rejected under 35 U.S.C. § 112, first paragraph, as allegedly failing to comply with the enablement requirement. The Examiner's argument relies, in part, on the assertion that claims to *in vivo* applications are not enabled by *in vitro* data. However, Applicants are not required to provide evidence of clinical or *in vivo* studies to claim methods of treatment: all that is required is a reasonable correlation between *in vitro* data and the claimed *in vivo* use. *See In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436, 1441 (Fed. Cir. 1995). The Examiner presents arguments that there may not be an exact correlation between *in vitro* results and claimed *in vivo* results. However, a rigorous or an invariable exact correlation is not required, as stated in *Cross v. Iizuka*, 753 F.2d 1040, 1050, 224 USPQ 739, 747 (Fed. Cir. 1985).

Moreover, the art provides evidence of RNAi *in vivo*. Xia *et al.* (Exhibit B) demonstrated that that adenoviral vectors expressing siRNAs against GFP, when administered into GFP-transgenic mice, results in specific silencing of targeted genes *in vivo* (Xia *et al.*,"siRNA-mediated gene silencing in vitro and in vivo," *Nature Biotechnology* 20: 20: 1006-1010 (2002)). McCaffrey *et al.* (Exhibit C) used a hydrodynamic transfection method to deliver naked siRNAs to the livers of adult mice and demonstrated that the expression of the respective target gene was significantly reduced (McCaffrey *et al.*, "RNA interference in adult mice," *Nature* 418: 38-39 (2002)). Accordingly, the present claims to *in vivo* uses are not inherently unbelievable based on the *in vitro* data, in view of the knowledge available in the art.

For at least these reasons, Applicants respectfully believe that the rejections under 35 U.S.C. § 112 have been accommodated, rendered moot or overcome. Applicants respectfully request reconsideration and withdrawal of the rejections.

VI. Rejections Under 35 U.S.C. § 101

At page 12 of the Office Action the PTO has rejected claim 20 under 35 U.S.C. § 101. In view of the foregoing amendments to the claims, it is believe that this rejection has been overcome. Applicants respectfully request reconsideration and withdrawal of the rejection.

VII. Rejections Under 35 U.S.C. § 102 and 35 U.S.C. § 103

At page 12 of the Office Action the PTO has rejected claims 20-27 and 37 under 35 U.S.C.§ 102(e) as being anticipated by U.S. Publication 2005/0245475 to Khvorova et al. (hereinafter "Khvorova"). At page 14 of the Office Action, the PTO has rejected claims 20-27 and 37 under 35 U.S.C. § 103(a) as being unpatentable over U.S. Publication 2004/0005565 to Bennett et al. (hereinafter "Bennett").

In view of the foregoing amendment to the claims, it is believed that the rejections have been overcome. The art cited by the Examiner does not describe and enable any of the sequences recited in the present claims. Accordingly, Applicants respectfully request reconsideration and withdrawal of these rejections.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that all of the pending claims are now in condition for allowance. An early notice to this effect is earnestly solicited. If there are any questions regarding the application, the Examiner is invited to contact the undersigned at the number below.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicants hereby petition for such extension under 37 C.F.R. §1.136 and authorize payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

Date March 12, 2007

By /Elliott/

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